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Chronic inflammatory factors and underlying causes in primary cutaneous marginal zone lymphoma

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Background

Primary cutaneous marginal zone lymphoma (PCMZL) is a low grade B cell lymphoproliferative disorder that has been included under the broader category of extranodal marginal zone lymphomas (ENMZL). However, the underlying pathogenesis is not well understood. Dermatopathology dogma states that reactive germinal centers are common in PCMZL.[1] It is unknown where marginal zone cells, which are the end product of germinal centers, come from. Furthermore, it is unknown what antigenic stimuli elicit the germinal center formation in the skin.

In a smaller case-control study published ten years ago, we reported on the incidence of gastrointestinal and autoimmune comorbidities of patients presenting with PCMZL.[2] In this retrospective chart review, we aim to validate our original findings in a much larger cohort of 246 patients. We report a detailed description of patient comorbidities as well as signs and symptoms related to chronic inflammation.

Methods

A retrospective chart review was conducted on 246 cases seen at our institution between 2007 and 2023. Out of the 246 total patients, 120 were seen at our institution and 126 were consult cases. Medical history was available for 168 patients.
We noted patient symptoms and co-morbidites, with particular attention to underlying infections, systemic cancers, and gastrointestinal or autoimmune conditions. We identified T1 cases possibly due to local trauma such as arthropod bites, tattoos, surgeries or vaccines. Lab results such as H pylori and Lyme serology, ANA, LFT's, SPEP, and UPEP were also noted.

Table 1. Medical Comorbidities and Laboratory Results

Medical Comorbidities (168 total patients with available medical history)

Gastrointestinal	N	%
GI History	93	55.40%
No GI History	75	44.6%
GERD	58	34.5%
IBD (Crohn's + UC)	7	4.2%
Crohn's	2	1.2%
Ulcerative Colitis	5	3.0%
Diarrhea	19	11.3%
Irritable Bowel Syndrome	16	9.5%
Peptic Ulcer Disease	8	4.8%
Diverticulitis	5	3.0%
Diverticulosis	5	3.0%
Colitis	5	3.0%
Gastritis	5	3.0%
Viral Hepatitis	4	2.4%
Non-alcoholic Fatty Liver Disease	2	1.2%
Lactose intolerance	4	2.4%

Autoimmune	N	%
Autoimmune History	48	28.6%
No autoimmune History	120	71.4%
Rheumatoid Arthritis	4	2.4%
Hashimoto's Thyroiditis	12	7.1%
Alopecia Areata	3	1.8%
Systemic lupus erythematosus	3	1.8%
Ulcerative Colitis	5	3.0%
Sjogren's	2	1.2%
Sicca Syndrome	5	3.0%
Skin - Related	11	6.5%
Psoriasis	4	2.4%
Vitiligo	3	1.8%
Lichen Planus	2	1.2%
Chronic Spontaneous Urticaria	2	1.2%
Bullous Pemphigoid	1	0.6%

Autoimmune	N	%
Other autoimmune Conditions	8	4.8%
Autoimmune hepatitis	2	1.2%
Myaesthenia Gravis	2	1.2%
Immune thrombocytic purpura	1	0.6%
Ankylosing Spondylitis	2	1.2%
Chronic Inflammatory Demyelinating Polyneuropathy	1	0.6%
Primary Sclerosing Cholangitis	1	0.6%
Vasculitis	1	0.6%
Mixed connective tissue disease	1	0.6%

Cancer		
Comorbid Cancer	60	63.0%
No comorbid Cancer	102	63.0%
Hematologic Cancer	7	4.3%
Lymphoma, Nodular Sclerosis	1	0.6%
Systemic Follicular (Non-Hodgkin)	2	1.2%
DLBCL	4	2.5%
Skin	44	27.2%
Other	28	17.3%
Prostate	9	5.6%
Breast	7	4.3%
Thyroid	3	1.9%
Endometrial	1	0.6%
Lung	2	1.2%
Bladder	2	1.2%
Giant cell tumor	1	0.6%
Renal	3	1.9%
Colon	1	0.6%
Pituitary	1	0.6%
Meningioma	1	0.6%
Nasopharyngeal	1	0.6%

Laboratory Results

ANA	N	%
Total Ordered	89	
Positive	57	64.0%
ANA 1:40	10	11.2%
ANA 1:80	10	11.2%
ANA 1:160	12	13.5%
ANA 1:320	8	9.0%
ANA 1:640	6	6.7%
ANA 1:1280	9	10.1%

H. Pylori Antibody	N	%
Total Ordered	106	
Positive	21	19.8%
Negative	85	80.2%

Lyme Antibody	N	%
Total Ordered	100	
Positive	1	1.00%
Negative	99	99.00%

SPEP	N	%
Total Ordered	101	
Positive	16	15.80%

UPEP	N	%
Total Ordered	47	
Positive	7	14.90%

Results

Of the 168 patients with available medical history, 55.4% (93) of patients had gastrointestinal comorbidities, including GERD, inflammatory bowel disease, irritable bowel syndrome, and peptic ulcer disease. 28.6% (48) of patients had comorbid autoimmune conditions such as Hashimoto's, Sjogren's, rheumatoid arthritis and lupus. 35.7% (60) had a comorbid cancer. Of the T1 cases, 22.5% (7/31) were possibly due to local trauma such as arthropod bites, tattoos, surgeries, and vaccines. Other notable comorbidities occasionally noted included leprosy (1), sarcoidosis (1), and hemochromatosis (1). Further detail can be seen in Table 1.

Regarding lab results, 64% (57/89) had a positive anti-nuclear antibody. 19.8% (21/106) had a positive H. pylori serology. Only 1% (1/100) had positive Lyme serology. 3.6% (6/168) had abnormal LFT's due to viral hepatitis or nonalcoholic fatty liver disease. 15.8% (16/101) of SPEP's and 14.9% (7/47) of UPEP's ordered revealed a monoclonal gammopathy.

Following treatment of comorbidities, we note 6 cases in which patients reported improvement of lesions following antibiotic therapy for H. pylori infection, and 1 case in which a patient achieved remission following control of ulcerative colitis.

Conclusions

Our results validate our original findings related to chronic antigenic stimulation in patients presenting with PCMZL. PCMZL is an indolent disease with excellent prognosis (99% five-year survival). Our data suggests that identifying and treating the underlying cause of the lymphoproliferative process may have a positive impact in the evolution and resolution of this condition.

References

1. Guitart J. Rethinking primary cutaneous marginal zone lymphoma: shifting the focus to the cause of the infiltrate. J Cutan Pathol. 2015 Sep;42(9):600-3. doi: 10.1111/cup.12509. Epub 2015 May 26. PMID: 26011667.
2. Guitart J, Deonizio J, Bloom T, Martinez-Escala ME, Kuzel TM, Gerami P, Kwasny M, Rosen ST. High incidence of gastrointestinal tract disorders and autoimmunity in primary cutaneous marginal zone B-cell lymphomas. JAMA Dermatol. 2014 Apr;150(4):412-8. doi: 10.1001/jamadermatol.2013.9223. PMID: 24500411.